Review and Evaluation of Clinical Data

Briefing Document for Psychopharmacological Drugs Advisory Committee Meeting

June 16, 2003

NDA: 19-758
Sponsor: Novartis
Drug: Clozaril (clozapine)
Subject: Agranulocytosis rates in the Clozaril National Registry (CNR)
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This document summarizes and evaluates the sponsor's analyses of the effect of white blood cell (WBC) count monitoring frequency on the rate of clozapine-associated agranulocytosis using data from Clozaril National Registry (CNR). In addition, the document summarizes the Office of Drug Safety consult on those reports.

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1. Background

Clozaril® (clozapine) was approved on September 26, 1989 for the indication of treatment resistant schizophrenia. Due to the potentially fatal adverse event of agranulocytosis, the Agency approved labeling that required weekly white blood cell count (WBC) testing prior to dispensing. The Clozaril National Registry (CNR) collects data from the WBC monitoring system.

Patients who develop agranulocytosis (ANC $\leq 500/mm^3$ or WBC $\leq 1000/mm^3$) or severe leukopenia (WBC $< 2000/mm^3$) during treatment are discontinued from therapy and deemed "non-rechallengable". The CNR maintains a list of all non-rechallengable patients, and new patients are crosschecked against this list prior to treatment initiation.

Previous analyses of CNR data for the Psychopharmacologic Drugs Advisory Committee (PDAC) on July 14, 1997 suggested that the agranulocytosis rate associated with clozapine use decreases substantially after the first six months of therapy[1]. Subsequent to this PDAC meeting, the Agency approved the following changes in WBC monitoring frequency on March 3, 1998:

"Patients who are being treated with Clozaril (clozapine) must have a baseline white blood cell (WBC) and differential count before initiation of treatment, and a WBC count every week for the first six months. Thereafter, if acceptable WBC counts (WBC greater than or equal to 3,000/mm^3, ANC$\geq$1500/mm^3) have been maintained during the first six months of continuous therapy, WBC counts can be monitored every other week. WBC counts must be monitored weekly for at least 4 weeks after the discontinuation of Clozaril (clozapine)."

On July 18, 2001, the sponsor[2] and the Division of Neuropharmacological Drug Products (DNDP) met to discuss the agranulocytosis rate observed following the implementation of the post-six month biweekly WBC monitoring program for Clozaril, which began in April 1998. At the time, there were no data available for discussion but the sponsor agreed to submit a Proposed Frequency Analysis Plan for review and comment. The analysis plan was submitted on November 5, 2001 and the sponsor was informed in March 2002 that the plan was acceptable.

This document summarizes the results of the analysis plan as submitted by the sponsor in its reports dated 9/9/2002, 10/8/2002, 2/12/2003, and 5/5/2003.

[1] Reference Dr. Judith Racoosin's 7/7/97 review of the sponsor's submission for the 7/14/97 PDAC - Appendix 1 and Novartis' PDAC briefing book dated 5/30/97

[2] Throughout this document the term "the sponsor" refers to Novartis Pharmaceuticals Corporation

2. The sponsor's stated objectives of the analyses

- To compare the effect of biweekly monitoring of WBC after six months of treatment with clozapine (started in April 1998) on the incidence rate of agranulocytosis and severe leukopenia with that of weekly monitoring of WBC (prevailed before April 1998).
- To estimate the additional risk of agranulocytosis and severe leukopenia if the WBC monitoring is further reduced to monthly monitoring or no monitoring after six months, one year or two years of treatment with clozapine.

3. Methods

3.1. Restrictions on CNR Data for Analysis

Since the introduction of generic clozapine in the US market in December 1997, Novartis, the innovator, no longer possesses WBC records for all clozapine-treated patients in the U.S. Therefore, the total exposure to clozapine could not be calculated based solely on CNR data. So, to estimate the incidence rate of agranulocytosis and severe leukopenia, the sponsor placed some restrictions on the data obtained from the CNR as follows:

1. Exclude all data for patients who were enrolled in CNR but never started treatment with clozapine or had only one record of WBC in the database (Approximately 22,000 patients were excluded).

2. Exclude all data for patients who started treatment with generic clozapine before any treatment with brand Clozaril® (Approximately 4,000 patients were excluded).

3. For patients started on brand Clozaril but switched to generic clozapine at some point in time -- exclude all data after the first treatment with generic clozapine (Approximately 19,000 patients were affected by this criterion).

3.2. Patient cohorts for analysis

To estimate the rates and ratios relevant to the objective of this analysis, the sponsor defined the following cohorts of patient population (graphically presented in sponsor's figure 1):

Cohort 1:
Cohort 1 includes data from approximately 97,000 patients. This cohort represents the group of patients who were included in the last briefing book submitted (April 28, 1997) to the Agency on frequency of WBC monitoring. It includes all patients who started brand clozapine between Feb 5, 1990 and April 30, 1995 (the cut-off date for that report). Cohort 1 includes the following five kinds of patients:

a) Patients discontinued brand clozapine treatment before April 30, 1995.
b) Patients continued brand clozapine beyond April 30, 1995, but discontinued before introduction of generic clozapine in December 1, 1997.

c) Patients continued clozapine beyond December 1, 1997, but discontinued before the initiation of bi-weekly monitoring in April 1, 1998.
d) Patients continued clozapine beyond April 1, 1998, but discontinued before September 1, 2001 (the new data cut-off date for the current Analysis).
e) Patients continuing treatment with brand clozapine on September 1, 2001.

Cohort 2:

Cohort 2 includes data from approximately 41,000 patients. This cohort represents all patients who initiated Clozaril therapy after the April 30, 1995 cut-off mentioned above but before the implementation of the biweekly monitoring after six months of treatment. It includes all patients who started brand clozapine after April 30, 1995 and before October 1, 1997 (six months before the introduction of biweekly monitoring option). This cohort includes the following three kinds of patients:

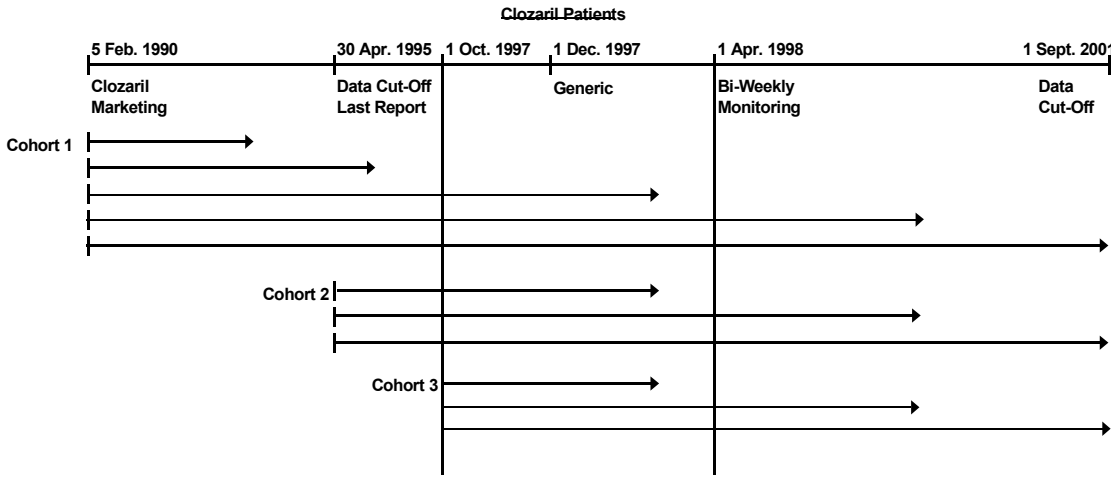
a) Patients discontinued brand clozapine treatment before April 1, 1998.
b) Patients continued on brand clozapine beyond April 1, 1998, but discontinued before September 1, 2001 (the new data cut-off date for the current Analysis).
c) Patients continuing treatment with brand clozapine on September 1, 2001.

Cohort 3:

Cohort 3 includes data from approximately 39,000 patients. This cohort represents patients who have been monitored according to the current monitoring system. It includes all patients who started brand clozapine after October 1, 1997 (six months before the introduction of biweekly monitoring option). This cohort includes the following three kinds of patients:

a) Patients discontinued brand clozapine treatment before April 1, 1998.
b) Patients discontinued brand clozapine treatment after April 1, 1998, but before September 1, 2001.
c) Patients continuing treatment with brand clozapine on September 1, 2001.

Sponsor's figure 1: Population Cohorts



It is worthy to note that cohorts 1 and 2 include patients that were treated with Clozaril during both the weekly monitoring period (prior to April 1, 1998) and the post six-month bi-weekly monitoring period (after April 1, 1998). As such, the rates of agranulocytosis and severe leukopenia, after the initial six months, were influenced by both monitoring schedules. Therefore, the Division requested that the rates of agranulocytosis and severe leukopenia in cohorts 1 and 2 be recalculated (separately and combined) using a cutoff date of March 31, 1998. This allowed us to compare the rates of agranulocytosis in the populations (cohorts 1 and 2) that had only weekly monitoring after six months with cohort 3, the population that had only biweekly monitoring after six months. Subsequently, the analyses of cohorts 1 and 2 presented in the reports dated 10/8/2002 and 2/12/2003 exclude data collected after March 31, 1998.

3.3. Actual rates of agranulocytosis, severe leukopenia, and moderate leukopenia

Using the cohorts defined as above, the sponsor calculated the incidence rates per 1000 patient-years for agranulocytosis (WBC <1000/mm^3 or ANC < 500/mm^3), severe leukopenia (WBC <2000/mm^3), and moderate leukopenia (WBC <3000/mm^3 or ANC < 1500/mm^3). These rates were calculated separately for the first six months of therapy and for the period subsequent to that because the rates have been observed to decrease markedly after the first six months of clozapine therapy.

The sponsor did not break out the agranulocytosis rate after six months into any smaller intervals. Previous analyses (see briefing package for 7/97 PDAC meeting, Appendix 1) suggest that the agranulocytosis rate continues to fall over the subsequent months and years before stabilizing. We wanted to determine if the same pattern occurred in the current set of cohorts being analyzed. For the agranulocytosis rates in the first six months, we divided the number of agranulocytosis cases occurring in that period by the exact amount of patient time accrued (as provided in post-text table 1.1-2a, 10/8/02 submission). To calculate the agranulocytosis rate for the 0.5-1 year interval and for each subsequent year interval, we used the information contained in the sponsor's life tables for each cohort (cohorts 1 and 2, post text tables 1.1-9a and 1.1-10a, 10/8/02 submission; cohort 3, post text table 1.1-11, 9/9/02 submission). All patients continuing into the next interval were assigned the full amount of time for that interval, and those patients discontinuing during the interval were assigned half the time of that interval (e.g., 3 months for the 6-month interval and 6 months for the 12-month intervals). The agranulocytosis rate for each interval was calculated as the number of cases identified during the interval divided by the total patient years of exposure during that interval. Patients in cohort 1 had a maximum of nine years of exposure; patients in cohort 2 had a maximum of three years of exposure; and patients in cohort 3 had a maximum of four years of exposure.[3]

[3] Recall that the exposure of patients in cohorts 1 and 2 is terminated artificially at April 1, 1998 in order to allow a comparison of weekly monitoring after six months to biweekly monitoring after six months. In actuality, some patients in cohorts 1 and 2 had longer exposures than nine years and three years, respectively.

3.4. Additional data requested by FDA

The agranulocytosis and severe leukopenia rates calculated in the section above showed a secular downward trend between cohorts 1-2 and cohort 3 for the initial six-month period, despite no change in monitoring during those first six months. In an effort to explain this secular trend, DNDP requested that the sponsor provide the following additional information in order to evaluate the potential impact of these factors on the observed incidence rates:

- Demographic information for patients in each cohort
- Median white blood cells count at the time of discontinuation for all patients in the Clozaril National Registry

3.4.1. Demographics

Summary statistics of the demographics (i.e., age, sex, and race) for all three cohorts as described above were provided.

3.4.2. WBC at discontinuation

- The WBC at the time of discontinuation for each patient was determined as follows:

  > "If a patient had a gap between WBC counts greater than 15 days during the first six months of therapy or a gap between WBC counts greater than 30 days after 6 months of therapy then the last WBC count prior to the date of discontinuation was used. For patients who discontinued on multiple occurrences then only the first point of discontinuation was utilized."

- Patients who discontinued (as defined above) with a WBC value between 3,000 to 6,000 were identified and median WBC values were compared for patients in Cohorts 1 and 2 (combined) and Cohort 3.

3.5. Projected rates of agranulocytosis and severe leukopenia

As part of the preparation for the July 1997 PDAC discussion of the clozapine WBC monitoring schedule, the sponsor modeled predictions for what might happen to the rates of agranulocytosis, severe, and moderate leukopenia should the monitoring schedule be made less frequent. The sponsor applied very similar modeling methodology to the Cohort 3 data to predict what might happen to the rates of agranulocytosis and severe and moderate leukopenia should the monitoring schedule be made less frequent again.

In order to determine the projected rates of agranulocytosis and severe leukopenia, the sponsor calculated the duration of the prodrome (period leading up to moderate leukopenia) and an estimate of the slope of WBC decline during the prodrome for each patient. Briefly, the onset of the prodrome was determined by examining data for WBC counts and determining the date from which the count showed a continual decline until moderate leukopenia (WBC $\leq 3000/mm^3$) developed, allowing for one possible increase in the count during that interval but only to a level that did not exceed the baseline count.

The method of estimation of rates of agranulocytosis and severe leukopenia if the current bi-weekly monitoring of WBC counts after six months of treatment with clozapine is changed to

a monthly schedule, or discontinued altogether is similar to the method of estimation of these rates for less frequent monitoring described at the 1997 PDAC meeting (Appendix 2).

Briefly, the projection of rates of agranulocytosis and severe leukopenia depends on the following four quantities estimated from data collected after six months of treatment:

1. P1 = Probability that a patient will develop severe leukopenia given that the patient was detected ("caught") at the moderate leukopenia stage ($2000/mm^3 < WBC \leq 3000/mm^3$).

2. P2 = Probability that a patient will develop agranulocytosis given that the patient was detected ("caught") at the moderate leukopenia stage ($2000/mm^3 < WBC \leq 3000/mm^3$).

3. P3 = Probability that a patient will develop agranulocytosis given that the patient was not detected ("missed") at the moderate stage (i.e. became severely leukopenic, WBC < $2000/mm^3$ by the time of detection).

4. P4 = Incidence rate (per person-year) of agranulocytosis among patients who did not have a WBC $\leq 3000/mm^3$ before developing agranulocytosis. These are the patients who developed agranulocytosis before they met the criteria for moderately leukopenic (i.e., missed at the moderate and severe stage).

The estimates of these four quantities based on data from Cohort 3 were deemed unreliable since the number of occurrences of agranulocytosis or severe leukopenia in Cohort 3 after six months of treatment was less than ten. Therefore, these four quantities were estimated using data from Cohorts 1 and 2 during their weekly monitoring of WBC.

Sponsor's table B illustrates the computation of the number of severe leukopenia and agranulocytosis cases that would be projected under a monitoring frequency program that was weekly for six months followed by monthly monitoring.

Sponsor's table B: Estimation of the number of severe leukopenia and agranulocytosis cases for patients in Cohort 3 after weekly monitoring for six months and monthly thereafter (source: submission dated 2/12/2003)

	Number of Patients with ≥6 months of treatment	Agranulocytosis rate	Estimated number of agranulocytosis cases	Estimated number of severe leukopenia cases
Moderate under the bi-weekly monitoring	230			
"Caught" at moderate under monthly monitoring	134	P2=0.021	134*P2=2.83	134*P1=3.5
"Missed" at moderate under monthly monitoring	96	P3=0.413	96*P3=39.68	96
Never moderate under the current monitoring	21974#	P4=0.000104	26696*P4=2.78	
Total	22204		45.29	99.5

#These patients were treated for 26696 person-years

The estimated number of agranulocytosis and severe leukopenia were computed if the monitoring was changed to monthly after one year and two years of treatment. The results are presented in sponsor's post-text table 4 (appendix 3) with the corresponding projected rates of agranulocytosis and severe leukopenia that would have been observed should the monitoring frequency be reduced to once monthly or no monitoring at all.

In order to compare the effect of a change in the monitoring system at different points in time (six months, one year, and two years), the estimated **cumulative number** of cases of agranulocytosis and corresponding rates per 1000 person-years after six months are presented in sponsor's post-text table 5 (appendix 3).

3.5.1. Reviewer's comment

- I note that the actual calculations of P1, P2, and P3 are based on persons and the calculation of P4 is based on person-years. This approach seems reasonable because those patients used to generate P4 are followed for a variable amount of time.

4. Results

4.1. Actual rates of agranulocytosis and severe leukopenia

At the time of data cut-off, 178,104 enrolled patients treated with table Clozaril were included in the primary analyses. Among these patients, 22 (0.012%) of them died due to

agranulocytosis, 593 (0.33 %) of them experienced agranulocytosis, and 658 (0.37%) of them developed severe leukopenia.

I summarized the findings reported by the sponsor in the following (source: sponsor's post-text Table 1.1-2a, submission dated 10/8/02 and post-text table 2, submission dated 2/12/2003):

	Cohort number *	# of cases/ patient year 0-6 months	Rate /1000 patient year 0-6 months	# of cases/ patient year >6 months	Rate /1000 patient year >6 months
Agranulocytosis (WBC 1000/mm^3 or ANC < 500/mm^3)	Cohort 1	315/41649	7.56	117/278324	0.42
	Cohort 2	78/16513	4.72	7/31305	0.22
	Cohort 3	46/14152	3.25	10/27020	0.37
Death from agranulocytosis&	Cohorts 1 & 2	18/58162	0.31	1/309629	0.003
	Cohort 3	2 /14152	0.14	1/27020	0.037
Severe leukopenia (WBC <2000/mm^3)	Cohort 1	321/41644	7.71	137/278265	0.49
	Cohort 2	82/16512	4.97	12/31304	0.38
	Cohort 3	48/14149	3.39	9/27017	0.33
Moderate leukopenia# (WBC <3000/mm^3 or ANC < 1500/mm^3)	Cohort 1	1286/41473	31.00	2387/272491	8.76
	Cohort 2	492/16444	29.92	319/30939	10.31
	Cohort 3	394/14093	27.96	214/26765	8.00

* Cohorts 1 and 2 had weekly monitoring after six months; Cohort 3 had biweekly monitoring after six months.
# Source: post-text table 2, submission dated 2/12/2003
& These rates were not provided by the sponsor, but the death counts were provided in their submission dated 2/12/2003

4.1.1. Reviewer's comments

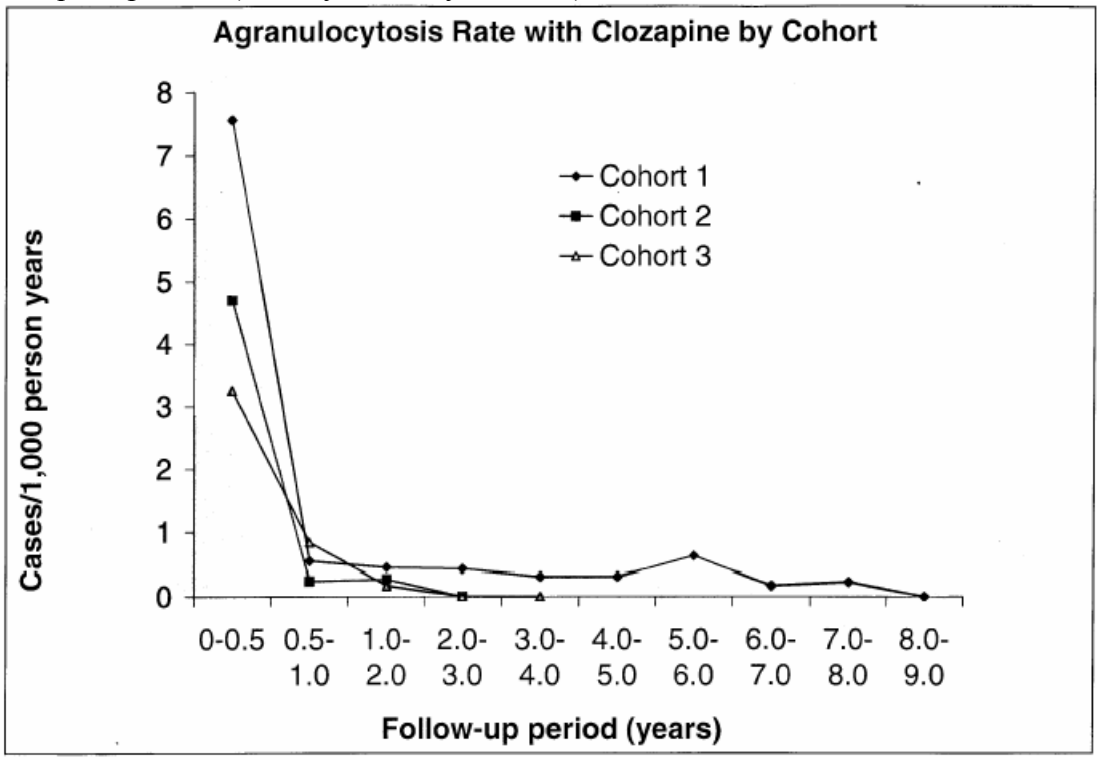
- Note that the incidence rate of agranulocytosis **during** the first six months for Cohorts 1, 2, and 3 were unexpectedly different given that all three cohorts were subjected to the same weekly monitoring during this period.
- The incidence rate of agranulocytosis **after** the first six months of treatment for Cohorts 1, 2 and 3 were also unexpected because it did not show that the risk was increasing with the bi-weekly monitoring as was projected.
- The rate of severe leukopenia showed a similar decline as observed with agranulocytosis during and after the first six months.
- The difference in incidence of agranulocytosis and severe leukopenia between cohorts 1 and 3 in the first six months, might speculatively be explained by the fact that as physician awareness of clozapine-associated agranulocytosis increased over the early-mid 1990's they tended to stop treatment or to temporary interrupt it if they noticed a downward trend in a patient's WBC count.
- Note that the rates of agranulocytosis per 1000 patient-years after six months went down from cohort 1 (0.42) to cohort 2 (0.22) then came up in cohort 3 (0.37). This might be a result of random variation or a trend that supports a slight increase in the rate after changing the monitoring frequency to bi-weekly. We should keep in mind that the comparison of the rates of agranulocytosis after six months in cohorts 1 (0.42) and 3 (0.37) is difficult to interpret because of the downward trend of the incidence rates in the first six months of treatment between cohorts 1 and 3.
- After the substantial decrease in agranulocytosis incidence after six months, the rate of agranulocytosis associated with clozapine use in cohort 3remains higher than the background rate of 3-7 cases/million person years[4,5].

[4] Kaufmann DW, Kelly JP, Levy M, Shapiro S. The Drug Etiology of Agranulocytosis and Aplastic Anemia. Oxford University Press 1991. Chapters 3, 8, 15.
[5] Kaufmann DW, Kelly JP, Jurgelon JM, et al. Drugs in the aetiology of agranulocytosis and aplastic anaemia. *Eur J Haematol* 1996; 57 (suppl): 23-30.

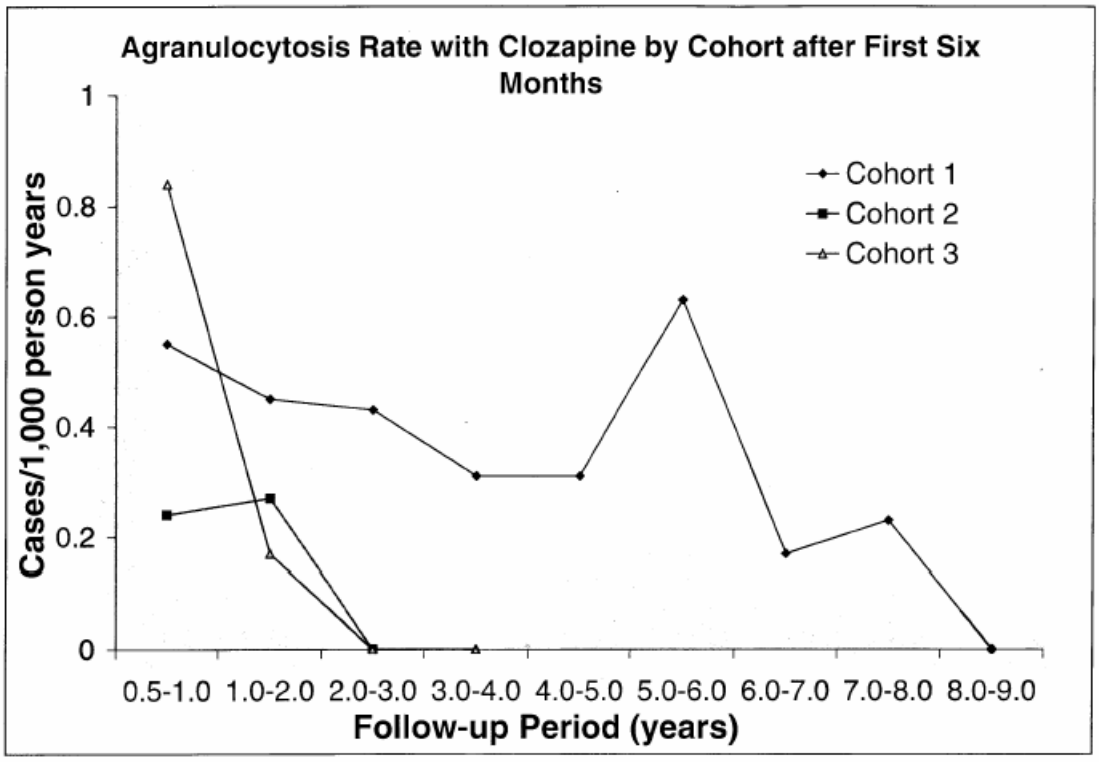
- The death rate before six months in cohort 3 is about half that of the combined cohorts 1 and 2. In contrast, the death rate in cohort 3 after six months is about 10 times higher than the earlier cohorts. However, the cohort 3 death rate is based on one case and thus is unstable.

4.2. Breakdown of agranulocytosis rates after six months

The figure below shows the agranulocytosis rates for the first six months and for the subsequent periods (0.5- 1 year, 1-2 years, etc.) for each cohort.



Because the rates after the first six months drop substantially, a second figure with an expanded y-axis shows the rates beginning at the second six months of therapy.



4.2.1. Reviewer's comments

- After six months, the agranulocytosis rates trended down in all three cohorts, although cohort 1 had a brief increase at year 5-6.
- The agranulocytosis rates going to zero in all three cohorts (at year 8-9 for cohort 1 and year 2-3 for cohorts 2 and 3) was associated with a substantial decrease in the size of the cohort (presumably related to switching to generic formulations). We will evaluate the WBC data from the generic companies to see if similar patterns of agranulocytosis rate decrease are observed after six months.

4.3. Demographics of patients in Cohorts 1 and 2 (combined) and Cohort 3

Sponsor's table 1 (submission dated 2/12/2003) below shows that the demographics of the patients within Cohorts 1 and 2 combined and Cohort 3 are similar with respect to sex, age, and race. The percentage of missing information was also similar between these groups.

Sponsor's table 1: Demographics of patients in Cohorts 1 and 2 (combined) and Cohort 3

Demographic	Category	Cohort 1 and 2 N (%)	Cohort 3 N (%)
Sex	Male	79256 (57.1)	22287 (56.8)
	Female	56430 (40.6)	16149 (41.1)
	Missing	3158 (2.3)	824 (2.1)
	Total	138844 (100)	39260 (100)
Age	<= 35	50124 (36.1)	12794 (32.6)
	36 - 50	53225 (38.3)	14808 (37.7)
	51 - 65	17474 (12.6)	6073 (15.5)
	> 65	14863 (10.7)	4761 (12.1)
	Missing	3158 (2.3)	824 (2.1)
	Total	138844 (100)	39260 (100)
	Mean	42.1	43.0
Race	White	95958 (69.1)	24528 (62.5)
	Black	17367 (12.5)	6058 (15.4)
	Hispanic	5819 (4.2)	2014 (5.1)
	Oriental	1725 (1.2)	460 (1.2)
	Other	1578 (1.1)	724 (1.8)
	Missing	16397 (11.8)	5476 (13.9)
	Total	138844 (100)	39260 (100)

4.3.1. Reviewer's comment

- Patients participating in the three cohorts are not different regarding their known attributes. Thus differences in the demographic make-up of the cohorts to the extent described above does not explain the discrepancy between those cohorts in the observed rates of agranulocytosis and severe leukopenia.

4.4. White blood cell count at time of discontinuation

In an effort to understand the secular decrease in the agranulocytosis rate over the three cohorts, despite the exact same monitoring schedule for the first six months in each cohort, we requested data on the WBC count at the time of patient discontinuation. We aimed to determine whether patients who appeared to have dropping WBC counts were discontinued at

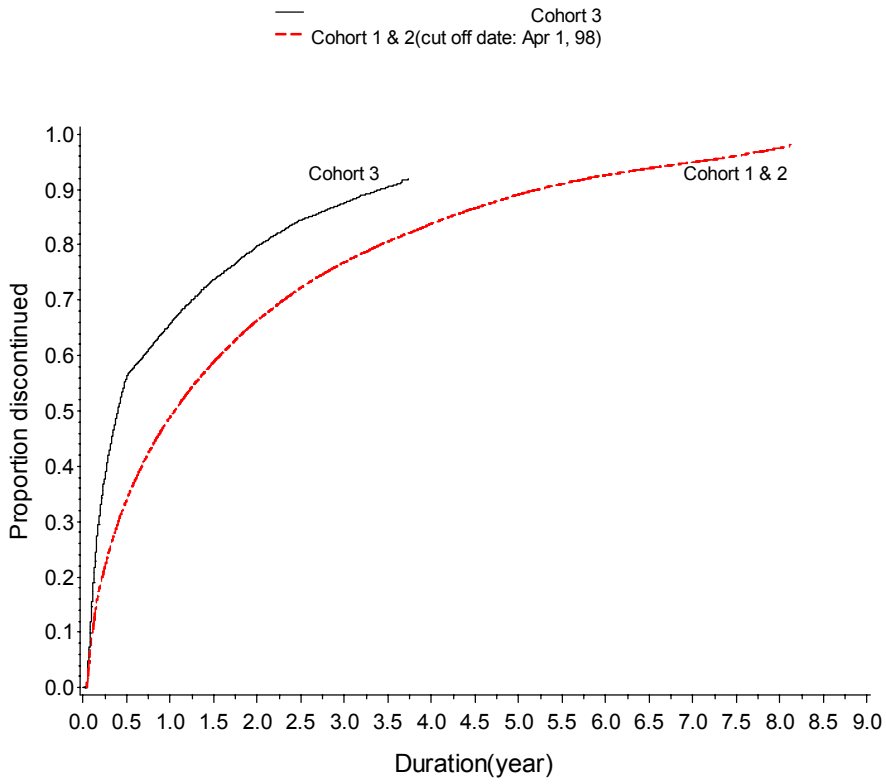
a higher WBC count in later years of the CNR (cohort 3) as compared to earlier years (cohorts 1 and 2). One factor hindering this analysis was the fact that the reason for a patient's discontinuation from the CNR is not recorded in the database. Thus there is no way to distinguish patients who discontinue for lack of efficacy or non-compliance from those who discontinue for a dropping WBC count (unless the patient develops severe leukopenia or agranulocytosis). As such, we have to consider the WBC count prior to discontinuation for all patients, and not just the ones we are interested in (those discontinuing due to a concern that their WBC count was falling).

There were 110,663 patients defined as patients who discontinued therapy. Of these patients, there were 56,986 who discontinued during the first six months of therapy and 53,677 who discontinued sometime after six months of therapy.

The median white blood cell count at the time of discontinuation for patients in Cohort 1 and 2 combined and Cohort 3 were 7700 and 7400, respectively, for patients on therapy for less than or equal to six months, and 7900 and 7500, respectively, for patients on therapy for more than six months (Sponsor's post-text Table 8, submission 2/12/2003). Additionally, there is no clinically meaningful difference between the groups with regard to the distribution (i.e., 5^{th}, 25^{th}, 75^{th}, 95^{th} percentiles) of WBC values at the time of discontinuation.

Sponsors' figure 1 shows that more than 50% of the patients in Cohort 3 discontinued therapy within 6 months after initiating therapy. In comparison, less than 35% of the patients in Cohorts 1 and 2 (combined) discontinued therapy within 6 months after initiating therapy.

Figure 1: Time to discontinuation
(Excluded patients data met criteria 1, 2 and 3)



The WBC values for patients who were discontinued with a WBC value between 3000 and 6000 were also evaluated. The sponsor justified its choice of the value of 3000 as this is the lower level of normal for WBC and presumably a value at which a Healthcare practitioner would discontinue a patient due to developing leukopenia. The sponsor choose the upper limit of 6000 because patients who were discontinued with a value above this level would be less likely to have been discontinued for a reason related to an abnormal WBC value and more likely for other reasons (e.g., availability of alternative treatment).

The median and mean WBC at the time of discontinuation for patients in Cohort 1 and 2 combined and Cohort 3 were similar for patients on therapy for less than or equal to 6 months and greater than 6 months (sponsor's table 2, submission dated 2/12/2003).

Sponsor's table 2: White Blood Cell Count (WBC) at time of discontinuation by duration for patients with WBC value between 3000 and 6000 at time of discontinuation (Cohort 1 and 2 combined and Cohort 3)

	≤6 months		>6 months		Total duration of therapy	
	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3
N	8325	4113	8833	1109	17158	5222
Median WBC	5300	5300	5300	5300	5300	5300
Mean WBC	5186	5154	5222	5180	5205	5160

Source: Post-text Table 9, submission dated 2/12/2003.

The proportions of patients who discontinued with values between 3000 and 6000 and within each stratum were similar between the groups. Over 60% of the patients in both groups were discontinued with a WBC value >5000-6000 regardless of duration of therapy (sponsor's table 3, submission dated 2/12/2003).

Sponsor's table 3: Stratified White Blood Cell Count (WBC) at time of discontinuation by duration for patients with WBC value at time of discontinuation (Cohort 1 and 2 combined and Cohort 3)

	Median WBC N (%)					
	≤6 months		>6 months		Total duration of therapy	
	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3
≥3000-4000	3800 531 (7%)	3800 299 (7%)	3800 477 (5%)	3800 56 (5%)	3800 1008 (6%)	3800 355 (7%)
>4000-5000	4700 2520 (30%)	4700 1260 (30%)	4700 2494 (28%)	4600 349 (31%)	4700 5014 (29%)	4700 1609 (31%)
>5000-6000	5600 5274 (63%)	5600 2554 (62%)	5600 5862 (66%)	5600 704 (63%)	5600 11136 (65%)	5600 3258 (62%)

Source: Post-text Table 10, submission dated 2/12/2003.

4.4.1. Reviewer's comment

- One hypothesis that might explain the secular decreasing trend in agranulocytosis rates from Cohort 1 to Cohort 3 would be increased physician awareness of clozapine-associated agranulocytosis by the late 90's (in comparison to the early 90's), if this awareness led to patients being discontinued at the first sign of declining WBC counts. Based on the data shown above, the distribution of WBC count at time of discontinuation does not suggest that patients were discontinued for reasons related to abnormal WBC values.

- Description of the demographics (age, gender, and race) of patients that discontinued in the first six months is missing. This might give an idea about potential differential pattern of discontinuation between various cohorts in a way that might explain the discrepancy between the rates of agranulocytosis and severe leukopenia in those cohorts.

- This analysis is may be flawed by the definition used for selecting the last WBC count prior to discontinuation.

  "If a patient had a gap between WBC counts greater than 15 days during the first six months of therapy or a gap between WBC counts greater than 30 days after 6 months of therapy then the last WBC count prior to the date of discontinuation was used. For patients who discontinued on multiple occurrences then only the first point of discontinuation was utilized."

Exploration of the data by one of the generic clozapine manufacturers identified that a substantial proportion of their patients had gaps in WBC count data the size of those used in the definition above. These gaps are due in many cases to non-compliance with the WBC monitoring as a result of the underlying schizophrenia (i.e., patient goes a few weeks without medication because they are non-compliant with their blood draw), but are not related to a true discontinuation of therapy. Because the definition used by the sponsor censors any WBC count data following the first 15 or 30 day (depending on the duration of their clozapine therapy) gap in data, this analysis approach could miss subsequent low WBC counts that truly led to discontinuation.

4.5. Projected rates of agranulocytosis and severe leukopenia

4.5.1. Prodrome and slope

As mentioned earlier, in order to determine the projected rates of agranulocytosis and severe leukopenia, the sponsor calculated the duration of the prodrome (period leading up to moderate leukopenia) and an estimate of the slope of WBC decline during the prodrome for each patient. Briefly, the onset of the prodrome was determined by examining data for WBC counts and determining the date from which the count showed a continual decline until moderate leukopenia (WBC $\leq 3000/mm^3$) developed, allowing for one possible increase in the count during that interval but only to a level that did not exceed the baseline count.

The median duration of prodrome ranged from 21-25 days and 26-29 days for patients in Cohorts 1 and 2 (combined) and Cohort 3, respectively (post-text Table 3.1, submission dated 2/12/2003) who were treated with Clozaril from >6 months to >2 years of therapy.

Sponsor's table 4 (submission 2/12/2003) provides below the median slope for patients with moderate leukopenia that did or did not develop agranulocytosis. In both cohort groups (cohort 1 and 2 combined, and cohort 3) patients who developed agranulocytosis during the first six months had WBC counts that declined faster than members of their respective cohorts who did not develop agranulocytosis. Also, patients who developed agranulocytosis during the first six months of therapy in Cohort 1 and 2 (combined) had a much steeper slope than those in Cohort 3.

This difference in the slope for the patients that developed agranulocytosis between these cohorts during the first six months of therapy may have contributed to the different incidence rates of severe leukopenia and agranulocytosis among these cohorts that we previously observed, because a steeper slope would decrease the likelihood that a patient would be identified as at risk ("caught") before they developed severe leukopenia or agranulocytosis.

Sponsor's table 4: Median slope for patients who developed moderate leukopenia and did or did not develop agranulocytosis

Duration of Therapy	Cohort 1 and 2 (combined) Median Slope (n)		Cohort 3 Median Slope (n)	
	Did not Develop Agranulocytosis*	Developed Agranulocytosis **	Did not Develop Agranulocytosis *	Developed Agranulocytosis **
≤6 mos.	150 (1444)	241 (334)	144 (366)	161 (28)
6 mos. – 1 year	135 (563)	244 (19)	126 (87)	71 (1)
1-2 years	161 (743)	150 (32)	121 (77)	None
>2 years	142 (2175)	156 (48)	167 (49)	-

Slope = decrease in WBC/day; *Source: sponsor's post-text table 3.3, 2/12/2003; **Source: sponsor's post-text table 3.2, 2/12/2003.

451...1. Reviewer's comment

- The observation that patients that developed agranulocytosis in cohorts 1 and 2 combined had a steeper slope of WBC fall (241) than those in the third cohort (161) provides some support for the possibility that physicians practicing in the late 1990's (during cohort 3) discontinued or temporarily stopped patients who had a rapidly declining WBC counts prior to them getting into the range of moderate/severe leukopenia and agranulocytosis.

4.5.2. Projected Rates

The report that was submitted on September 9, 2002 included 39,260 patients from Cohort 3 in the primary analysis. Among them approximately 22,000 patients were treated for more than six months with brand Clozaril. Any alternative monitoring option of WBC after six months of treatment with Clozaril would have affected these patients in Cohort 3. Sponsor's table 5 summarizes actual and projected number of cases of severe leukopenia and agranulocytosis after weekly monitoring during the first six months of therapy followed by bi-weekly, monthly or no monitoring among Cohort 3 patients. It should be noted that the number of severe leukopenia and agranulocytosis cases provided in Table 5 are based, in part, on the calculations shown in sponsor's table B in the same submission (2/12/2003).

Sponsor's table 5: Actual and projected number of cases of severe leukopenia and agranulocytosis after weekly monitoring during the first six months of therapy followed by bi-weekly, monthly, or no monitoring (Cohort 3 patients)

	Change to bi-week monitoring after weekly monitoring for:	Actual Cases Observed	Projected Additional Cases with Monthly Monitoring	Projected Additional Cases with No monitoring
Severe Leukopenia	Six months	9	91	221
	One year	5*	56	123
	Two years	4*	16	46
Agranulocytosis	Six months	7	38	150
	One year	2*	26	86
	Two years	0*	9	34

*Assumes that bi-weekly monitoring still occurs (i.e., no change from current monitoring system)
Source: Post-text Tables 4 and 6, 2/12/2003

As seen in sponsor's table 5, if the current monitoring was changed to "monthly monitoring" **after six months** then we would observe 91 additional cases (as compared to the number

observed with biweekly monitoring) of severe leukopenia and 38 additional cases of agranulocytosis, and 221 and 150 additional cases of severe leukopenia and agranulocytosis, respectively, if "no monitoring" was in place.

- After six months of therapy, bi-weekly monitoring is currently required and the actual observed rate[6] of agranulocytosis is **0.26/1000** person-years. Based on the projections in sponsor's table 5, the rate of agranulocytosis would increase to **1.68/1000** person-years if the monitoring frequency was decreased to monthly intervals and increased to **5.81/1000** person-year if monitoring was discontinued (source: post-text table 5, submission dated 2/12/2003, appendix 3).

If the current monitoring was changed to "monthly monitoring" **after one year** then we would observe 56 additional cases of severe leukopenia and 26 additional cases of agranulocytosis, and 123 and 86 additional cases of severe leukopenia and agranulocytosis, respectively, if "no monitoring" was in place.

- Based on the projections in sponsor's table 5, the rate of agranulocytosis would increase to **1.21/1000** person-year if the monitoring frequency was decreased to monthly intervals and increase to **3.43/1000** person-year if monitoring was discontinued (source: post-text table 5, submission dated 2/12/2003, appendix 3).

If the current monitoring was changed to "monthly monitoring" **after two years** then we would have observed 16 additional cases of severe leukopenia and 9 additional cases of agranulocytosis, and 46 and 34 additional cases of severe leukopenia and agranulocytosis, respectively, if "no monitoring" was in place.

- Based on the projections in sponsor's table 5, the rate of agranulocytosis would increase to **0.6/1000** person-year if the monitoring frequency was decreased to monthly intervals and increased to **1.52/1000** person-year if monitoring was discontinued (source: post-text table 5, submission dated 2/12/2003, appendix 3).

4.5.3. Reviewer's comment

- When the projection methodology was applied at the July 1997 PDAC meeting to predict what might happen if the WBC monitoring schedule was stretched out further, the prediction was that changing from weekly to biweekly after six months would result in an agran rate of 0.9/1000 patient years (as compared to what had been the observed rate of 0.54/1000 patient years after six months on weekly monitoring). In contrast, what has been observed in cohort 3, is an actual decrease over time to 0.37/1000

[6] This rate is lower than 0.37/1000 patient-years shown in the table in section 4.1 because the sponsor excluded three cases who stopped treatment with clozapine prior to six months but subsequently developed agranulocytosis after six months

- Based on the above data, the sponsor concluded that the predictions of the additional risk due to further reduction of monitoring based on their projection methodology were "unreliable and misleading". As such, they did not initially submit any projections of number and risk of agranulocytosis or severe leukopenia cases for a monthly or no monitoring scenario. Subsequently, the Division requested that they adjust their projection methodology to take into consideration what had actually happened with the agranulocytosis rate. Because it was difficult to identify with any certainty the factors which led to the decrease in the agranulocytosis rate (when an increase had been expected), the sponsor submitted the current projections using a very similar methodology as that used in the 1997 analysis.
- For logistical reasons, the sponsor's analysis is limited to patients who started and remained on brand clozapine; if patients started on brand clozapine and then switched to generic, only their time on brand clozapine is counted in the analysis. Because we don't know what selection factors may determine which patients are more likely to stay on brand clozapine or switch to a potentially less expensive generic version, the sponsor's projections may not be generalizable to the total population of clozapine users. We have requested agranulocytosis rate data and demographic data from the two main generic manufacturers of clozapine in order to assess the comparability of the populations of generic and brand users. .

4.6. Projected number of fatal outcomes related to agranulocytosis

As of September 2001, there were 22 fatalities of patients who developed agranulocytosis as recorded in the CNR. Among them, 20 patients developed agranulocytosis within the first six months of Clozaril therapy. Only 3 of the 22 fatalities occurred in patients from Cohort 3 and 2 of these 3 occurred during the first six months of treatment.

The estimated additional number of deaths for patients in Cohort 3 is presented in sponsor's post-text table 7 (submission dated 2/12/2003). If the monitoring system was changed to once monthly after six months of therapy, 1 to 6 additional deaths due to agranulocytosis would have been observed. The corresponding number of additional deaths for no monitoring system after six months is 5 to 22. The data is presented as a range because of the underlying assumption about the range of mortality from agranulocytosis.

5. Sponsor's comments

- The rates of moderate leukopenia that are provided with the current analysis are similar between the two groups and demonstrate that the current monitoring system (bi-weekly

monitoring after six months) provides a level of patient safety that is equal to the previous monitoring system.

- Careful monitoring of patients in the first six months with the current system continues to be warranted.
- There have been 22 fatalities since the introduction of monitoring in US. Of these fatalities, four took place since the implementation of the current bi-weekly monitoring schedule. This fact alone emphasizes the need for vigilance in monitoring to minimize the risk to patients.
- Since the monitoring procedure was the same (i.e., weekly) for the first six months for all three cohorts, the rates of agranulocytosis and severe leukopenia should have been similar. However, the agranulocytosis and severe leukopenia rates for Cohort 3 were less than one-half that for Cohort 1. The sponsor hypothesized a number of possible explanations for this lack of comparability for the rates within the first six months. These include:

  1. Increased awareness of agranulocytosis by the providers.
  2. The decreased percent of new patients, since a significant portion of the agranulocytosis cases are seen during the first six months of treatment.
  3. It is possible that for patients who started on generic clozapine and subsequently switched to Clozaril, the data during the first six months of generic clozapine therapy would not have been available for the analysis. This would result in the exclusion of data during the highest risk period (first six months of therapy) of agranulocytosis and a reduction in the risk of agranulocytosis for this cohort.
  4. The steady decline in the agranulocytosis incidence rate per 1000 patient-years by calendar year since 1990.
  5. Given the similar rates of moderate leukopenia between the two groups (cohort 1and 2 combined and cohort 3), the lower rate of agranulocytosis between the groups that we previously observed may be due to other factors (e.g., discontinuation of patients, medical advancements in the treatment of leukopenia, alternative therapies for the treatment of schizophrenia) that can not be considered when utilizing models to estimate the number of additional agranulocytosis cases under alternative monitoring frequency systems.

  However, the sponsor has not been able to determine with the current data in the CNR whether any of the possible explanations are responsible for the inconsistent first six months results.

- The projections in sponsor's table 5 demonstrate that there will be substantial increases in the number of agranulocytosis cases with changes in the current monitoring system; however, the validity of these projections should be taken in context with the projections provided in 1997. The projected rate for cohort 3 (111/67661, 0.00164) based on the 1997 analysis was 5.29 times than that actually observed for cohort 3 (7/22209, 0.00031). Clearly there are variables (e.g., medical advancements in the treatment of leukopenia, alternative therapies for the treatment of schizophrenia) influencing the development of agranulocytosis that can not be considered in the projection model.

5.1. Reviewer's comments

- The sponsor provided a number of possible explanations for the observed decrease in agranulocytosis rate between cohorts 1 and 2 combined and cohort 3 despite identical monitoring frequencies within the first six months. The sponsor's points 2 and 4 refer to "decreased percent of new patients" and "steady decline in the agranulocytosis incidence…by calendar year". This reasoning explains the decline in agranulocytosis incidence by calendar year because the pool of the patients most susceptible to agranulocytosis (i.e., new users) was shrinking each subsequent calendar year. However, the agranulocytosis rate in the first six months of use includes only new users, so it is not affected by the declining proportion of new users/total users.
- In point 3 above, the explanation that patients "who started on generic clozapine and subsequently switched to Clozaril" might be responsible for the apparent reductions is not applicable because those patients were actively excluded from the studied cohorts.
- I agree with the sponsor about the difficulty on relying on the calculated rate projections.

6. Foreign data (UK and Australia)

The sponsor submitted a brief report describing the rates of agranulocytosis, severe leukopenia and moderate leukopenia in the US, Australia, and the UK (Appendix 4). Although there are some differences between the monitoring systems (e.g., in the US a patient who develops moderate leukopenia may be rechallenged once the WBC count recovers whereas a similar patient in the UK goes on the "non-rechallengable list"), it is informative to examine the agranulocytosis and severe leukopenia rates at the monthly monitoring frequency that Australia and the UK employ. The table below displays the monitoring schedules for each of the countries.

	Weeks 0-18	**Weeks 19-52**	**Weeks 52+**
Australia	Weekly	Monthly	Monthly
UK	Weekly	Biweekly	Biweekly pre-1995 Monthly post-1995
US	**Weeks 0-26** Weekly	**Weeks 26+** Weekly pre-1998; biweekly post-1998	

The report recalculated the US data for comparability purposes. The sponsor structured the data from the three countries to reflect the rates in the first 18 weeks, weeks 19-52 and weeks > 52 (so as to match up with the monitoring schedule in the UK).

	Weeks 0-18	Weeks 19-52	Weeks >52
Australian Data			
Severe Leukopenia {per 1,000 pt. Yrs. (N)}	12.7 (40) weekly	1.6 (8) monthly	0.7 (19) monthly
Agranulocytosis {per 1,000 pt. Yrs. (N)}	8.3 (26) weekly	2.2 (11) monthly	0.5 (14) monthly
United Kingdom Data			
Severe Leukopenia {per 1,000 pt. Yrs. (N)}			
Pre-1995 (monitoring frequency)	33.5 (58) weekly	4.3 (11) bi-weekly	2.6 (17) bi-weekly
Post-1995 (monitoring frequency)	31.9 (186) weekly	4.0 (34) bi-weekly	1.9 (58) monthly
Agranulocytosis {per 1,000 pt. Yrs. (N)}			
Pre-1995 (monitoring frequency)	24.8 (43) weekly	1.2 (3) bi-weekly	0.3 (2) bi-weekly
Post-1995 (monitoring frequency)	20.4 (119) weekly	1.5 (13) bi-weekly	0.6 (18) monthly
United States Data			
Severe Leukopenia {per 1,000 pt. Yrs. (N)}			
Pre-1998 (monitoring frequency)	8.8 (369) weekly	1.0 (66) weekly	0.4 (117) weekly
Post-1998 (monitoring frequency)	4.1 (43) weekly	0.7 (9) weekly/bi-weekly	0.3 (5) bi-weekly
Agranulocytosis {per 1,000 pt. Yrs. (N)}			
Pre-1998 (monitoring frequency)	8.8 (366) weekly	0.8 (50) weekly	0.4 (101) weekly
Post-1998 (monitoring frequency)	3.8 (40) weekly	1.0 (14) weekly/bi-weekly	0.1 (2) bi-weekly

N – number of events

As seen in the table above, in the UK data, the monitoring changed in 1995 from bi-weekly to monthly after week 52 of treatment. It is worthy to note that the rates of severe leukopenia and agranulocytosis are stable over time as shown in the largely comparable rates before and after 1995. After 52 weeks of treatment, the rates of severe leukopenia (per 1000 person years)

were 2.6 and 1.9 before and after 1995, respectively; the rates of agranulocytosis were 0.3 and 0.6 before and after 1995, respectively. These rates were consistent with the rates observed in the Australian database of severe leukopenia (0.7) and agranulocytosis (0.5) under monthly monitoring after week 52.

In the US data, the monitoring schedule changed in 1998 from weekly to biweekly after six months. For the monitoring period "weeks > 52", the rates of severe leukopenia (per 1000 person years) were 0.4 and 0.3 before and after 1998, respectively; the rates of agranulocytosis were 0.4 and 0.1 before and after 1998, respectively.

6.1. Reviewer's comments

- Unlike the US data, the UK data reflect a stable pattern of rates of severe leukopenia and agranulocytosis over time (i.e. before and after 1995).
- The rates reported in the foreign data do not suggest higher rates after reduction of monitoring from weekly to bi-weekly. However, there was an increase in agranulocytosis rate from bi-weekly to monthly in the period "weeks > 52", although it was based on small numbers.
- No information on the death rates in the foreign monitoring systems was provided so it is difficult to judge if there is any increase in mortality associated with reduced monitoring.

7. Office of Drug Safety consult

Dr Parivash Nourjah, an epidemiologist in the Office of Drug Safety (ODS), reviewed the data submitted by the sponsor, with a focus on the projection methodology. Dr Nourjah is speculating several reasons for the apparent decrease of rates of agranulocytosis and severe leukopenia in the initial period of six months from cohort 1 to cohort 3. In her evaluation, she considers that the two of the most probable explanations for the observed reduction of agranulocytosis risk are the following:

- The increased knowledge about and experience of health providers with the risk factors associated with agranulocytosis induced by clozapine.
- The increased knowledge about the factors related to a better response to clozapine.

Dr Nourjah asserts that there are three issues that limit using CNR data to project what would happen to the risk of agranulocytosis if the frequency of monitoring changes from biweekly to a lesser monitoring frequency:

- the unknown comparability of the cohorts,
- the unknown representativeness of patients in the cohorts to patients using generic clozapine
- the stability of estimates due to small case numbers.

She proposes that these factors limit the utility of the CNR data because using a biased or unreliable database to project the incidence rates under lesser monitoring frequency (e.g., monthly or not at all) may result in an erroneous conclusion and a wrong policy for managing the risk of agranulocytosis. Under this situation, she suggests using projected estimates for the worst-case and best-case scenarios as a frame of reference for discussion of change of policy. According to her calculations, under the worse cases scenario (with "no monitoring" policy), the agran incidence rate would get as high as 8.6 cases per 1000 patient-years. Under the best-case scenario (with the current biweekly monitoring), the incidence rate of agran is 0.26 cases per 1000 patient years.

7.1. Reviewer's comments

- I agree with the ODS reviewer about the limits on the use of the CNR data because of the reasons stated above.
- The "worst-case" scenario given by the ODS reviewer puts an upper limit on the rate of agranulocytosis (after six months) after correcting for the rate of decline in the first six months between cohort 2 and 3 assuming no monitoring. The calculated rate is higher than the one observed in the first six months even in cohort 1, which had the highest rate among the three cohorts. This high "worst-case" rate results, in part, from Dr. Nourjah's assumption that every patient who develops moderate leukopenia will progress to agranulocytosis; this assumption was not bourne out in the experience of the cohort 1 and 2 members who were treated for > six months (of the 75 patients who were not "caught" at the moderate leukopenia level, 41% went on to develop agranulocytosis). Another assumption here is that the observed numbers reflect the risk among the patient population using brand clozapine. Projecting the worst case scenario using these numbers may not be accurate given that the users of generic clozapine may differ from the users of the brand formulation. In addition, the real reasons for the decline in the first six months across the three cohorts is not readily understood and thus is difficult to correct for them numerically.
- The ODS reviewer's calculations does not explore possible scenarios for changing the monitoring system from bi-weekly to monthly.

8. Appendix 1 1997 DNDP Briefing package

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 7, 1997

FROM: Judy Racoosin, M.D., M.P.H.
Division of Neuropharmacological Drug Products
HFD-120

TO: File: NDA 19-758

SUBJECT: Review of Preparation Materials for Advisory Committee Meeting concerning the WBC Monitoring Schedule for Patients on Clozapine Therapy

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Summary

Due to the substantial increased risk of agranulocytosis (agran) observed in the clinical development program for clozapine, U.S. approval was contingent upon weekly mandatory white blood cell (WBC) count monitoring for each patient, effectively creating a registry of all clozapine users in the U.S. From registry data provided by Novartis, we calculated agran rates by time since first use for patients included in the Clozaril National Registry from November 1989 through April 30, 1995. Agran rates peaked in the first six months of patient use at 8.6 cases per 1000 person-years and then rapidly decreased to 0.7 cases per 1000 person-years over the 6 month - 2 year period from first use. Over the 2-3.5 year period, the rate declined to 0.4 cases per 1000 person-years, and to 0.2 cases per 1000 person-years in the 3.5-5.5 year interval. While the rate of 0.52 cases per 1000 person-years observed over the period of 6 months - 5.5 years from first use is 100 times the background rate in the general population, it is within the range of agran rates seen with other drugs marketed in the U.S., including ticlopidine and sulfasalazine. A risk analysis performed by Dr. Noel Weiss projected that with a change to no monitoring of WBC counts after 6 months of weekly monitoring, the incidence rate of agran would increase over 6 times, from 0.52 to 3.3 cases of agran per 1000 person-years. The incidence of agran in this scenario is within the range observed with other marketed drugs in the U.S. that do not require mandatory testing.

A. Background

The clinical development program of Clozaril™ (clozapine) identified agran as a serious adverse event associated with the use of the drug. When Clozaril™ was approved for

U.S. use on September 26, 1989, the FDA approved labeling required that the drug only be available through a distribution system that ensured weekly WBC testing prior to the delivery of the next week's supply of medication.[7] The Clozaril National Registry collects data from the WBC monitoring system. Previous analyses of the registry data identified that the agran rates decrease substantially after the first six months of therapy. Because of the significant decline in agran risk after six months of use, the question of whether to make changes in the WBC monitoring requirements is being taken to the Psychopharmacologic Drugs Advisory Committee.

In preparation for the Advisory Committee meeting, (1) the medical literature on drug-induced agran was reviewed, (2) current drug labeling for products with a warning for agran was reviewed, (3) the Clozaril National Registry data was reanalyzed, and (4) the sponsor's submission that provided a hematologic risk analysis was reviewed.

B. Methods

1. Review of the Literature

A Medline search was performed with the key terms agranulocytosis, drug-induced, and epidemiology. Only English language articles were reviewed. Specific drugs considered to induce agran were also searched. Reference lists from journal articles were cross-checked for other applicable references. In three references I estimated person-time exposure from tables or charts in order to generate approximate agran rates in those cohorts.[8,9,10]

Medline was also searched with the key terms agranulocytosis, mortality, and schizophrenia to identify sources of data that might address the incidence of agran and mortality from hematological disorders in the schizophrenic patient population.

2. Review of Drug Labeling

The CD-ROM version of the 1997 Physician's Desk Reference (PDR) was searched for medications that are labeled for agran. The search identified 294 drugs that contain agran in the warning, precaution, or adverse reactions sections of the labeling. The scope of the review was limited to only those drugs that listed agran in the

[7] Physician's Desk Reference, Sandoz Pharmaceuticals, March 1996.

[8] Furusawa S, Ohashi Y, Asanoi H. Vesnarinone-induced granulocytopenia: incidence in Japan and recommendations for safety. *J Clin Pharmacol* 1996; 36: 477-481.

[9]Keisu M, Ekman E. Sulfasalazine associated agranulocytosis in Sweden 1972-1989; clinical features, and estimation of its incidence. *Eur J Clin Pharmacol* 1992; 43: 215-218.

[10]Jick H, Myers MW, Dean AD. The risk of sulfasalazine- and mesalazine-associated blood disorders. *Pharmacotherapy* 1995; 15(2): 176-181.

warning section, as this subset of drugs was assumed to have the highest risk of causing agran. The labeling of these drugs was then reviewed to summarize the data on the incidence of agran in their clinical trials and to survey their WBC monitoring recommendations.

3. Analysis of Clozapine Agranulocytosis Data[11]

The calculation of clozapine agran rates prepared by the sponsor broke the follow-up period into 0-6, 7-12, 13-18, 19-24, and >24 month intervals. Because we wanted to break down the >24 month interval further, we obtained the life table data the sponsor used in their hematologic risk analysis report. This data set included data grouped by period of follow-up, age, and sex. For each follow-up interval, the sponsor included the number of agran cases, the number of patients censored during that interval, and the number of patients left at the end of the interval. From this life table data we calculated the person-years of exposure time[12], and subsequently the rate of agran in each follow-up interval. We then condensed the intervals into 11 6-month periods spanning the 5.5 years of registry data and recalculated the agran rates. After examining the case counts and person-year exposure for each six month block, we regrouped the follow-up period into the following strata: 0-6 months, 6 months-2 years, 2-3.5 years, and 3.5-5.5 years. These strata detail the fall in agran rates over the full follow-up period. In the recalculation of the agran rates, the rate unit was converted from cases per 100,000 person-weeks (used by the sponsor) to cases per 1,000 person-years, since the latter is a more standard unit for describing rates. Poisson regression was used to generate 95% confidence intervals for the point estimates.

We also used Poisson regression to analyze the effects of age and sex on the agran rate. The life table data provided by the sponsor included an age category of <40 years and >40 years and a sex category. We used likelihood ratio tests to compare hierarchical models. The likelihood ratio test compares a more complex model to a simpler model to determine if the additional variable or variables in the more complex model explain(s) more of the deviance (similar to variance).

4. Critique of Dr. Weiss's Risk Analysis

Dr. Noel Weiss's projections of agran rates under alternative WBC monitoring schedules initiated at varying times are described and his methods for arriving at those projections are evaluated. Poisson regression was used to generate 95% confidence intervals for his projected rate estimates. Again, the rate unit was converted from cases per 100,000 person-weeks to cases per 1,000 person-years.

[11] Dr. Greg Burkhart assisted with this analysis.
[12] We assumed that patients discontinuing in an interval contributed time equal to half the interval.

C. Results

1. Agranulocytosis Background Rates

a. General Population

Agran is a blood dyscrasia that primarily and predominantly affects the granulopoietic cell compartment and leads to severe neutropenia in an individual with a previously normal blood count. Patients with agran frequently present with acute, severe febrile infections that are due to the severe neutropenia. The definition of agran excludes patients with chronic neutropenias, leukopenia related to cytotoxic drugs or irradiation, or nonselective neutropenias due to systemic diseases (i.e. systemic lupus erythematosus, hypersplenism).[13] A laboratory-based definition of agran often utilizes a neutrophil count of less than or equal to $<0.5 \times 10^9$/L (also referred to as 500 neutrophils/ mm^3). However, the exact cutoff level varies from study to study.

An early estimate of the incidence of agran derives from a study of all patients discharged from the hospital with a diagnosis of a blood dyscrasia in the Uppsala health care region of Sweden during the years 1964-1968.[14] The investigators reviewed medical records for each patient to ensure the accuracy of the discharge diagnosis. The incidence of all-cause agran (defined in this paper as <180 neutrophils/mm^3) was 12.8 cases/ million persons/year.

The most comprehensive study of agran was the International Agranulocytosis and Aplastic Anemia Study (IAAAS), a population-based case control study involving eight sites in Europe and Israel. Case-patients had to present with symptoms such as fever, chills, or sore throat, and a neutrophil count <500 cells/mm^3. The overall rate of agran identified in this study was 4.7 cases/million persons/year[5]. The rate among the different geographic sites ranged from 1.7-7.0 cases/million persons/year. Increasing age and female sex were identified as risk factors for the disease.[5] An extension of the IAAAS, including one of the prior sites in Sweden and two new sites in the U.S., found the rate of agran to be 3.4 cases/million/year.[15]

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[13] Kaufmann DW, Kelly JP, Levy M, Shapiro S. The Drug Etiology of Agranulocytosis and Aplastic Anemia. Oxford University Press 1991. Chapters 3, 8, 15.

[14] Bottiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *Br Med J* 1973; 3: 339-343.

[15] Kaufmann DW, Kelly JP, Jurgelon JM, et al. Drugs in the aetiology of agranulocytosis and aplastic anaemia. *Eur J Haematol* 1996; 57 (suppl): 23-30.

A study utilizing a Medicaid billing database to estimate the incidence of agran included data from Minnesota, Michigan, and Florida. The diagnoses of agran were based on hospital discharge diagnoses and verified by primary medical record review. The overall incidence rate excluding recurrent or chronic neutropenia was 7.2 cases/million persons/year (95% CI: 6.3-8.1). The individual rates by state ranged from 2.3-15.4 cases/million persons/year.[16] Despite different approaches to estimate the incidence of agran and different populations studied, the background rate in the general population appears to be around 3-7 cases/million persons/year.

b. Schizophrenic Population

Despite an in depth search of the medical literature, we could locate no data describing the background rate of agran in the schizophrenic population. However, since a treatment-resistant schizophrenic may have exposure to some medications that may exert a toxic effect on the bone marrow, it would not be surprising if the background risk of agran in treatment-resistant schizophrenics was greater than that in the general population.

2. Agranulocytosis Associated with Specific Drugs

A search of the CD-ROM version of the 1997 PDR identified the following drugs as having warnings for agran in their labeling: bepridil, captopril (and all ace inhibitors), carbamazepine, clozapine, dapsone, fosphenytoin, levamisole, methimazole, mirtazapine, norfloxacin, ofloxacin, penicillamine, promethazine, procainamide, propafenone, sulfasalazine (and all sulfonamides), ticlopidine, and tocainide. Carbamazepine, clozapine, procainamide, ticlopidine, and tocainide have boxed warnings for agran. Agran associated with dapsone, fosphenytoin, levamisole, methimazole, norfloxacin, ofloxacin, penicillamine, and procainamide will not be discussed further because details concerning the risks of agran with those drugs were not described in the labeling or in the medical literature. The agran experience with mianserin and vesnarinone, two drugs not approved in the U.S., are described below because the rates are based on sufficient data. The risk[17] and rates[18] of agran associated with the drugs described below are summarized in Table 1.

Ticlopidine, an anti-platelet drug used in the treatment of stroke and approved in the U.S., was considered to cause agran and mild to moderate neutropenia at substantial rates in the clinical trials. The risk of agran (<450 neutrophils/mm^3) was 0.8% (17/2048), while the risk of mild-moderate neutropenia (451-1200 neutrophils/mm^3)

[16] Strom BL, Carson JL, Schinnar R, Snyder ES, Shaw M. Descriptive Epidemiology of Agranulocytosis. *Arch Intern Med* 1992; 152: 1475-1480.

[17] Risk refers to the number of events divided by the number of people at risk for the event.
[18] Rate refers to the number of events divided by the amount of person-time exposure.

was 1.6% (33/2048).[19] In the clinical trials, most of the cases of agran occurred within the first two months of therapy. Of the 74 cases of agran reported to FDA in pre- and post-marketing surveillance, the median duration of ticlopidine use prior to the development of agran was 30 days (personal communication). Ticlopidine labeling recommends monitoring the patient's CBC and white blood cell differential every two weeks for the first three months of therapy.[9]

Sulfasalazine, a treatment for inflammatory bowel disease, as well as for rheumatologic conditions, has been associated with agran. The first estimation of the incidence of sulfasalazine-associated agran was based on a series of cases reported to the Swedish Adverse Drug Reactions Advisory Committee between 1972 and 1989.[3] Agran was defined as a neutrophil count less than or equal to 0.5×10^9/L. The cases were validated with the original medical records; denominator data was based on an average prescribed daily dose that was calculated from pharmacy records. The investigators calculated the rate of agran as 0.6 cases/ 1000 person-years. I approximated total person-years of sulfasalazine exposure from the distribution of the estimated length of sulfasalazine treatment in 34,500 patients (Figure 2 of the article). The rate of agran in this cohort based on my estimation of person-time was 3 cases per 1000 person-years over the first year; however, the rate was as high as 10 cases per 1000 person-years in the 2-3 month period after initiating sulfasalazine therapy.

Jick et al studied the risk of sulfasalazine-associated agran in the United Kingdom's General Practice Research Database, a database generated by primary care physicians who supply medical information on their patients for research purposes.[4] Agran was defined as a neutrophil count less than or equal to 0.5×10^9/L. The investigators calculated the risk of agran as 0.68 cases per 1,000 users (95% CI: 0.33-1.4). I used the number of recorded prescriptions (Table 4 of the article) to estimate person-years of drug use. Based on my person-time estimate, the rate of agranulocytosis was 3 cases per 1000 person-years. The labeling for sulfasalazine warns that deaths from agran have been reported with the use of the drug and suggests that CBCs be done frequently in patients receiving sulfasalazine.[20]

Vesnarinone, a positive inotropic agent used in the treatment of symptomatic chronic heart failure, is approved for use in Japan. A clinical trial of the drug in the U.S. noted that 2.3% (20/912) of patients developed neutropenia (neutrophil count $<1.0 \times 10^9$)[21]; subsequently the incidence of this adverse event was studied in the population of Japanese patients prescribed the drug. This study of vesnarinone-induced

[19] Physician's Desk Reference, 1997 Edition. Roche Pharmaceuticals, August 1995.

[20] Physician's Desk Reference, 1997 Edition. Pharmacia & Upjohn, July 1994.

[21] Feldman AM, Pepine CJ, Bristow MR, et al. Incidence of vesnarinone induced neutropenia: the U.S. Experience. *Circulation* 1993; 88(4) Pt. II: I-301.

granulocytopenia[22] included a figure depicting the number of granulocytopenia cases and number of patients on vesnarinone therapy for each two week period of drug treatment. I used this data to estimate person-time and calculate agran and granulocytopenia rates for the cohort. Of 14,921 exposed patients, 89 (0.6%) developed granulocytopenia (<1,000 neutrophils/mm^3); 38 (0.25%) of these patients fulfilled their definition of agran (<100 neutrophils/mm^3). Based on my estimate of 21,310 person-years drug exposure, the incidence of granulocytopenia and agran in this population was 4.2 and 1.8 cases per 1000 person-years, respectively.[2] The authors recommended that patients on vesnarinone have at least weekly WBC count monitoring.

Carbamazepine has been implicated as a cause of agran. In the IAAAS, this drug was used by 1.5% of the cases and 0.2% of the controls, leading to a stratified relative risk estimate of 8.8 (95% CI: 2.7-29) and a multivariate relative risk estimate of 11 (95% CI: 1.9-62).[5] If one applies the relative risk to the background rate observed in the IAAAS, then the estimated rate of agran associated with carbamazepine is approximately 0.05 cases per 1000 person-years. The carbamazepine labeling suggests that the vast majority of minor hematologic changes observed in the monitoring of patients are unlikely to signal the occurrence of agran. However, the sponsor does recommend pretreatment hematologic testing and further states that a patient should be monitored closely if they exhibit a low or decreased WBC count in the course of treatment (though no formal WBC monitoring recommendations are offered).[23]

Mianserin, a tetracyclic antidepressant, was approved for use in New Zealand in December 1979. Post-marketing surveillance by the New Zealand Intensive Medicines Monitoring Programme (IMMP) identified an association between mianserin use and agran. Between 1983 and 1989, they studied the occurrence of this adverse reaction. The risk of agran was calculated using the total number of reports of agranulocytosis to the IMMP as the numerator; and an estimate of people at risk based on mean dose, mean duration of therapy, and pharmaceutical sales figures as the denominator. Over the five year study period, the IMMP estimated the risk of mianserin-associated agran as 0.74 per 1000 patients.[24]

Mirtazapine, a sister compound of mianserin, is approved in the U.S. for the treatment of depression. In its clinical development program, two cases of agran (hospital admission for infection and neutrophil count < 0.5×10^9) and one case of severe neutropenia (neutrophil count < 0.5×10^9) were observed over 671.7 person-years of drug exposure, leading to a rate of 4.5 cases per 1000 person-years.[25] One of the

[22] The term granulocytopenia used in this reference is synonymous with neutropenia.
[23] Physician's Desk Reference, 1997 Edition. CibaGeneva, May 1996.

[24] Coulter DM and Edwards IR. Mianserin and agranulocytosis in New Zealand. *Lancet* 1990; 336: 785-787.

[25] NDA 20-415, Clinical Review, October 19, 1995.

patients had a history of Sjogren's syndrome and a multisystem hypersensitivity reaction (dermatitis and hepatitis) concomitantly with the agran. The drug labeling recommends that if a patient develops signs of infection, along with a low WBC count, treatment with mirtazapine should be discontinued and the patient should be closely monitored.[26]

Captopril, an angiotensin converting enzyme inhibitor used for the treatment of hypertension and congestive heart failure, has been observed to cause neutropenia (defined as <1000 cells/ mm^3) in clinical trials. However, the incidence of this adverse event depended on the patient's clinical status. In patients with normal renal function being treated for hypertension, the risk of neutropenia was 0.11 cases per 1000 patients (1/8600). In patients with renal dysfunction (defined as a serum creatinine > 1.5 mg/dl), the risk of neutropenia was about 2 cases per 1000 patients. Patients with renal dysfunction and a history of collagen vascular disease were at the highest risk for developing captopril-associated neutropenia; in the clinical trials, 3.7% of this subgroup of patients developed this adverse reaction. The captopril labeling recommends that patients with impaired renal function have WBC and differential counts at approximately two week intervals for about three months, then periodically. The labeling suggests that captopril should be used with caution in patients with collagen vascular disease or in those who are taking other drugs known to affect white blood cells or immune response. Finally, the labeling recommends that all patients who are taking captopril should be warned to report any signs of infection.[27]

Bepridil, an antiarrhythmic drug approved in the U.S., was associated with marked leukopenia and neutropenia (no definitions given in the labeling) in its clinical trials. Two patients out of 800 developed these adverse reactions, leading to a risk of 2.5 per 1000 patients. The labeling does not include any WBC monitoring suggestions.[28]

Propafenone, an antiarrhythmic drug approved in the U.S., was considered to be "probably related" to a case of agran occurring in its U.S. clinical trials. In the course of over 800,000 patient-years of exposure during marketing outside the U.S. since 1978, seven additional cases of agran have been reported. Thus the observed rate of agran was 0.009 cases per 1000 person-years. The labeling recommends that patients should be instructed to promptly report the development of any signs of infection such as fever, sore throat, or chills; however, no specific WBC monitoring is suggested.[29]

[26] Physician's Desk Reference, 1997 Edition. Organon.

[27] Physician's Desk Reference, 1997 Edition. Bristol Myers Squibb.

[28] Physician's Desk Reference, 1997 Edition. McNeil Pharmaceuticals.

[29] Physician's Desk Reference, 1997 Edition. Knoll Laboratories, September 1992.

The labeling for tocainide, an antiarrhythmic drug approved in the U.S., states that agran and sequelae such as septicemia and septic shock have been reported in patients receiving the drug, mostly within the first three months of therapy. However, no estimate of agran risk or rate is included. There is a recommendation for weekly monitoring of complete blood counts, including WBC, differential, and platelets for the first three months of therapy, though.[30]

Phenothiazines have been long considered to induce agran. Most of the data on the incidence of this adverse drug reaction come from case series described in the 1950's and 1960's. The risk for phenothiazine-associated agran ranges from 0.004 - 6.8/1000 patients, depending on the case series.[31] However, in the IAAAS, phenothiazine use did not differ significantly between cases and controls..

3. Rates of Agranulocytosis with Clozapine Observed During Post-marketing Surveillance

In the U.S. through April 30, 1995, there were 406 agran cases over 158685.7 person-years of clozapine exposure. Despite weekly WBC monitoring, there were twelve deaths due to agran in the U.S. cohort of Clozaril users through April 30, 1995, accounting for 3% of all agran cases. All deaths occurred in patients on the drug for three months or less; 10/12 (83%) deaths occurred in patients over 40. In the U.K. cohort (through July 1994), the two deaths that occurred were also in patients on the drug less than three months.

Figure 1 depicts the rate of agran with clozapine over the full 5.5 year follow-up period. The agran rate peaks in the 0-6 month period at 8.6 cases per 1000 person-years; however, this rate is an average over the six months of that interval. The sponsor's Figure A (page 28 of the briefing book) depicts a peak in the hazard rate between 2-3 months at 29.1 cases per 1000 person-years that is three times higher than the average rate over the first six months since first use. The agran rate then falls rapidly in the 6 month-2 year period since first use to 0.7 cases per 1000 person-years. Because the rates after six months are low, it is difficult to show the confidence intervals without changing the y-axis scale. Therefore Figure 2 shows the rates of agran after six months on an expanded y-axis. The rates continue to fall all the way out to the last time period, 3.5 to 5.5 years, when there are 0.2 cases per 1000 person-years. Table 2 summarizes the rates with their 95% confidence intervals for each follow-up period.

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[30] Physician's Desk Reference, 1997 Edition. Astra Merck, July 1995.

[31] Anderman B and Griffith RW. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur J Clin Pharm* 1977; 11: 199-201.

When we modeled the agran rates, adding a variable into the model that divided time since first clozapine use into 4 strata (0-0.5 years, 0.5-2 years, 2-3.5 years, and 3.5-5.5 years) helped to explain the agran rate decrease over time (p=.03)[32]. However, time since first use of clozapine did not explain as much of the rate decrease when it was added into a model that already included patient age (p=.06)[6], suggesting that the evidence for a decline in rate may be somewhat model dependent. Interestingly, the actual estimate of agran rates by time since first use did not change substantially when either age and/or sex were added into the model.

The rate of agran was 2-3 times higher in the >40 as compared to the <40 group throughout the entire follow-up period, although the absolute rates for both were substantially higher in the 0-0.5 year interval as compared to the 0.5 - 5.5 year intervals. Table 3 summarizes the case counts and agran rates for the age and treatment duration strata.

4. Dr. Weiss's Hematologic Risk Analysis

The hematologic risk analysis performed by Dr. Weiss for the sponsor had two goals. The first was to summarize the incidence of agran and consequent mortality observed in the U.S. and U.K. Clozaril WBC monitoring systems in order to identify a subgroup of patients who might be at a low enough risk of agran to consider a reduced frequency of monitoring. The second goal was to project the additional incidence of agran and subsequent mortality for U.S. patients, given alternative schedules for WBC monitoring implemented at different times.

Since the sponsor focuses on changes in the WBC monitoring schedule after six months of Clozaril use, Dr. Weiss based his risk analysis on changes in that period. Among 581 patients who developed at least moderate leukopenia after six months of therapy, Dr. Weiss identified two groups. Patients in the first group were detected at moderate leukopenia (2000-3000 neutrophils/mm^3). Patients in the second group had already proceeded through moderate leukopenia and were detected at more severe leukopenia (500-2000 neutrophils/mm^3). The proportion of patients advancing to agran differed between the two groups. Specifically, the patients who had been detected at more severe leukopenia progressed to agran at a rate six times that of the patients detected at moderate leukopenia (45.2% vs. 6.7%).

By characterizing the pattern of declining WBC counts (what is later called a "prodrome") in patients with moderate leukopenia, Dr. Weiss projected what percentage of patients would be detected at a stage of moderate leukopenia under alternative WBC monitoring schedules. However, the assumptions needed to make these projections were not discussed. First, it appears that Dr. Weiss derived the percentage of patients who would be detected at moderate leukopenia from the

[32] These p-values have no inferential value.

distribution of prodrome lengths, assuming that the distribution would remain constant, regardless of a change in the monitoring schedule. Second, the criteria for defining the starting point of the prodrome were not explained. Finally, it was unclear whether characterization of the prodrome was based on only those patients with moderate leukopenia, or whether those patients first detected at severe leukopenia were also included.

Dr. Weiss determined that the median length of the prodrome (time to moderate leukopenia) was 21 days, but that in 25% of patients the prodrome was as short as 14 days. Apparently using the distribution of time to moderate (and possibly severe leukopenia), he estimated that under a proposed **biweekly** monitoring schedule, 73% percent of patients would have their leukopenia detected in the moderate range, while under a **monthly** monitoring schedule, 42% would be detected in the moderate range.

Once Dr. Weiss generated the number of patients who would be detected at moderate leukopenia for each proposed monitoring schedule change, he multiplied that number by the percentage who progressed on to agran (6.7%). In this way he calculated an estimate of the number of patients detected at moderate leukopenia who would develop agran under each of the alternative monitoring schedules. Those patients with leukopenia detected in the severe range were assumed to progress to agran at the higher rate (45.2%).

Table E of the risk analysis presents the number of agran cases projected to occur after a change from weekly monitoring to biweekly, monthly, or no monitoring schedules. Under Dr. Weiss's set of assumptions described above, his worst case scenario would be that the rate of agran would increase 6-7 times under a policy of no monitoring as compared to what has been observed with weekly monitoring. Figure 3 depicts the upper 95% confidence limit for each projected rate, along with the point estimate, converted into rate units of cases per 1000 person-years.

D. Discussion

Overall, there is substantial evidence that the occurrence of agran in the general population is a rare event on the order of a few cases per million per year. However, there are no data upon which to compare the background rate in schizophrenics to that in the general population.

By far, the best set of data in which to consider drug-induced agran is the Clozaril National Registry. There are enough data for only a few other drugs (ticlopidine, sulfasalazine, mianserin, and vesnarinone) to give reliable estimates for agran risk. In fact, among the drugs labeled with warnings for agran, the quality of the data from which agran risk or rates are calculated varies substantially. Some of the data comes from clinical trials where the rate or risk may be based on very few cases (i.e. bepridil, mirtazapine), whereas some clinical trials had a high enough incidence of agran to

generate a reliable estimate of agran risk (i.e. ticlopidine). At the same time, some of the estimates of agran risk derive from in-depth post-marketing surveillance programs that accumulated many cases (i.e. sulfasalazine, mianserin). The strongest labeling concerning the risk of agran for any of these drugs was a boxed warning with guidance for WBC monitoring. Clozapine is the only drug with mandatory WBC monitoring.

In addition to the variable quality of the data on agran risk, the definition of agran varies from drug to drug. Many studies utilized a cell count definition of <500 neutrophils/mm^3, while some used other cell count cut-offs (i.e. mianserin, vesnarinone, ticlopidine). Additionally, some studies did not describe agran per se, but amassed all the cases into a neutropenia category (i.e. captopril). Finally, some required that a patient have clinical illness along with a low neutrophil count (i.e. mirtazapine).

Our reanalysis of the 5.5 years of data on agran observed in the Clozaril National Registry reconfirms the peak incidence in the first six months of therapy and the subsequent decline thereafter identified by the sponsor. However, we also found that between the 6 month - 2 year interval and the 3.5 - 5.5 year interval, the agran rate fell by more than threefold. However, the rate observed even in this last follow-up period is approximately 100 times the background agran rate in the general population.

Dr. Weiss's hematologic risk analysis sought to project the expected agran rates under alternative WBC monitoring schedules of biweekly, monthly, and none implemented 6 months, 1 year, or 2 years following the initiation of clozapine therapy. He based his projections on the premise that the time to moderate leukopenia would not change with changes in the monitoring system, an untestable assumption. Additionally, it may be difficult to reliably define the start of the prodrome, possibly making the results of the risk analysis sensitive to the assumptions used to define the prodrome length. Because of the lack of information in the submission, we could not perform a sensitivity analysis to evaluate this latter concern in more depth.

In summary, given the worst case scenario described by Dr. Weiss of switching to no monitoring after six months of weekly monitoring, the projected rate of agran is 3.3 cases per 1000 person-years, with an upper confidence limit of 3.6 cases per 1000 person-years. This rate is within the range of rates observed ticlopidine and sulfasalazine.

E. **Conclusion**

This review describes the agran rates observed with clozapine over a 5.5 year period of follow-up and puts these rates into context with the agran risk and rates observed with other drugs marketed in the United States. Novartis suggests that without the WBC monitoring system, the agran rate would increase six-fold. Given this projection, the agran rate would be within the range of risk observed for ticlopidine and sulfasalazine.

Judith A. Racoosin, MD, MPH

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Table 1. Rate or Risk of Agranulocytosis and Neutropenia Associated with Specific Drugs
(see text for references)

Drug	Rate per 1000 person-years (# of cases)	Risk per 1000 persons (# of cases)	Comment	WBC Monitoring Recommendation
Clozapine	8.6 (n=340) 0.56 (n=66)		over 1st 6 mos of therapy from 6 mos - 5 yrs of therapy data from Clozaril National Registry	WBC count q wk
Ticlopidine		8 (n=17) 16 (n=33)	for agran (<450 /mm3) for neutropenia (450-1200 /mm3) data from clinical trials	WBC count q 2 wks X 3 mos
Sulfasalazine	3* 3*	0.57 (n=63) 0.68 (n=7)		CBC should be done frequently
Captopril		0.11 (n=1) 2 37	rates are for neutropenia (<1000/mm3) pts with normal renal function pts with serum creatinine >1.5 mg/dl pts with serum creatinine >1.5 mg/dl collagen vascular disease	Patients with impaired renal function should have WBC count q 2 weeks X 3 months, then periodically; all pts should report signs of infection;
Bepridil		2.5 (n=2)		No formal monitoring recommendations
Propafenone	0.009 (n=7)			Pts should report signs of infection;
Phenothiazines		0.004 - 6.8	range derived from 11 case series	No formal monitoring recommendations

* rate is based on a person-time denominator estimated from a table or graph in the reference

Table 2. Rates of Agranulocytosis with Clozapine over 5.5 years

Time Since First Exposure	Rate/1000 person-years	95% CI - Lower	95% CI - Upper
0 - 6 months	8.6	7.73	9.6
6 months - 2 years	0.7	0.50	0.9
2 - 3.5 years	0.4	0.23	0.7
3.5 - 5.5 years	0.2	0.05	0.7

Figure 1. Rate of Agranulocytosis with Clozapine over a 5.5 Year Follow-up

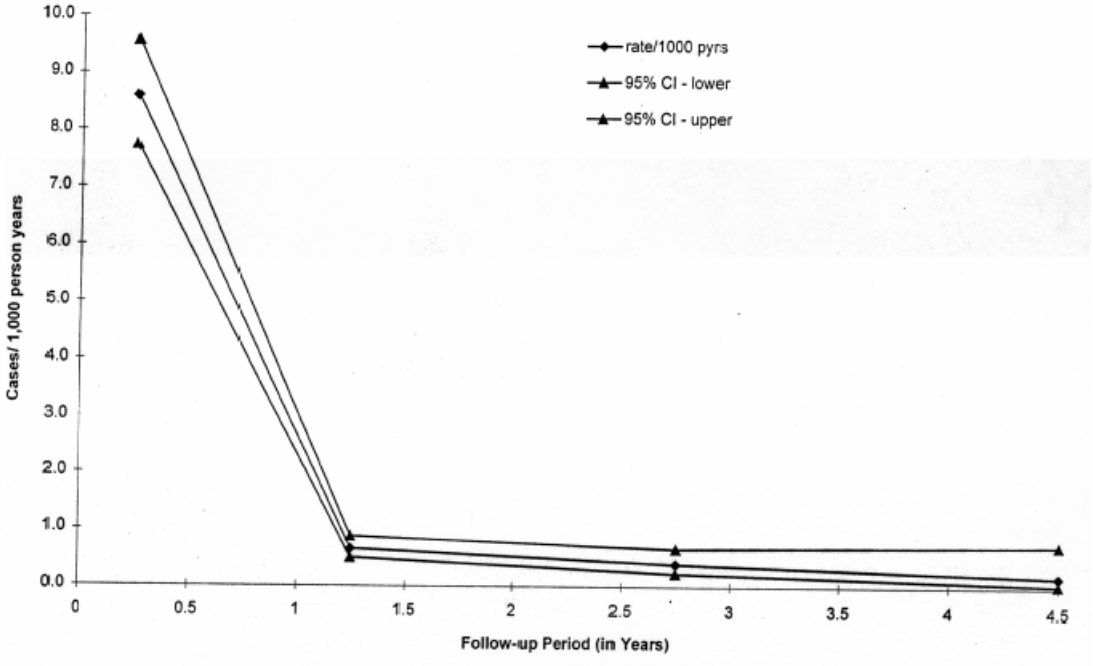


Figure 2. Rate of Agranulocytosis with Clozapine From 6 Months to 5.5 Years of Follow-up

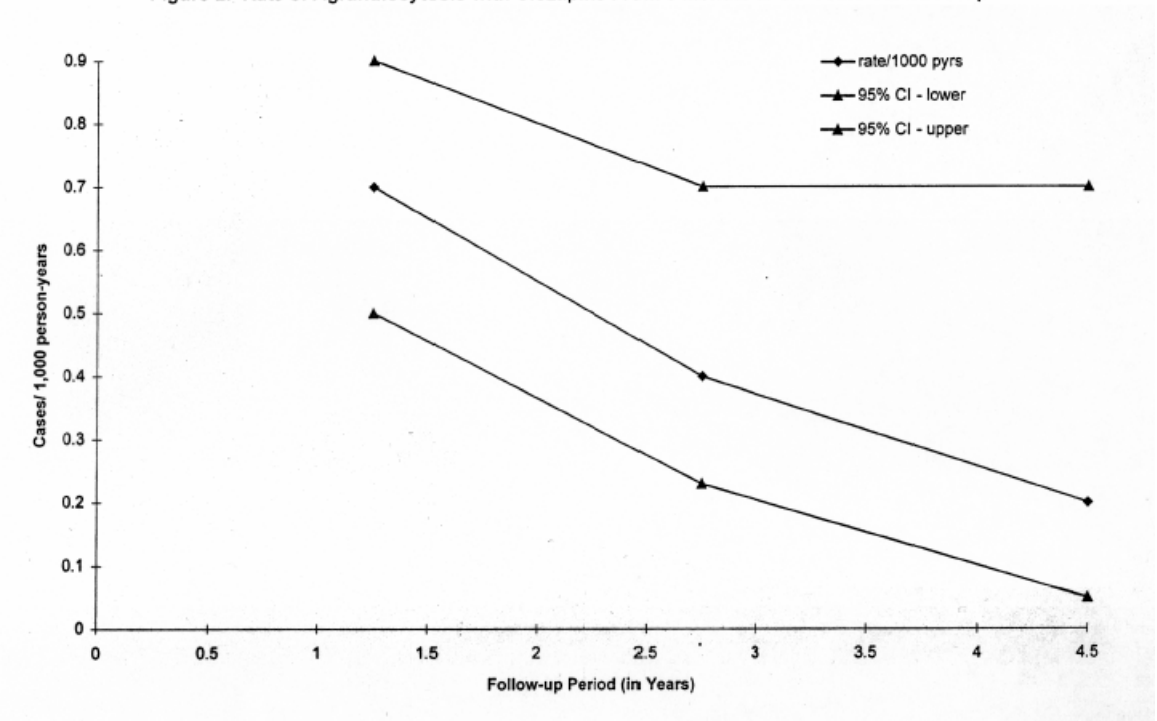
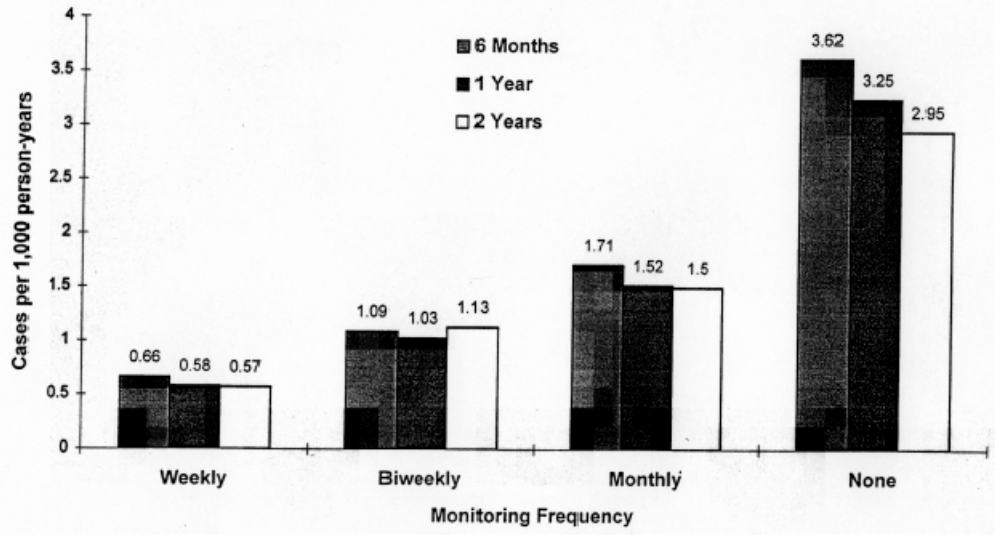


Table 3. Clozapine Agranulocytosis Cases by Age and Treatment Duration

Age	Treatment Duration	Cases	Person-years	Agran Rate per 1000 person-years
<40	0 - 6 months	109	23626	4.6
	6 months - 5.5 years	30	81663	0.4
>40	0 - 6 months	231	15921	14.5
	6 months - 5.5 years	36	40339	0.9

Figure 3. Upper 95% Confidence Interval of the Projected Rates of Agranulocytosis with Clozapine, Based on Weekly, Biweekly, Monthly, and No WBC Monitoring Initiated after 6 Months, 1 Year, and 2 Years of Weekly Monitoring (in cases/1000 person-years)



9. Appendix 2 Sponsor's method for estimating rates

Method for Estimating the Rates of Agranulocytosis and Severe Leukopenia if the Current Bi-weekly Monitoring Option of WBC Counts After Six Months of Treatment with Clozaril is Changed to a Less Frequent Monitoring Option

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Introduction

On October 15, 2002 Novartis and the Food and Drug Administration (FDA) met to discuss the Advisory Committee meeting regarding the frequency of monitoring for Clozaril-treated patients that is scheduled on February 28, 2003. During this meeting, the FDA requested that we develop a model that would estimate the incidence of agranulocytosis if monitoring were reduced in frequency or discontinued. The recommendation was to develop a model that was similar to the one that was outlined in the Briefing Book for the Psychopharmacological Drugs Advisory Committee held on July 14, 1997, which was submitted on April 28, 1997 (NDA No. 19-758).

This analysis plan is being provided as a supplement to our monitoring frequency analysis plan that was submitted on November 5, 2001 (NDA No. 19-758).

Principle

The method that will be used to estimate the rates of agranulocytosis and severe leukopenia if the current bi-weekly monitoring of white blood cell counts (WBC) that occurs after six months of treatment with Clozaril is changed to monthly or no-monitoring is based on the methods outlined in the above-mentioned briefing book. The rates will be estimated for patients in Cohort 3 only who are defined in our monitoring frequency analysis plan (Attachment 1) referenced above.

Data

All relevant data from Cohorts 1 and 2 who are defined in our monitoring frequency analysis plan (Attachment 1) referenced above will be used to compute relevant rates and ratios mentioned in Figure C (Attachment 2). All relevant data from Cohort 3, subject to exclusion criteria 1, 2, and 3 and data cut-off date of September 1, 2001 will be used for projection of rates for patients in this cohort.

Method

Step 1: Combined data from Cohorts 1 and 2 contains information on Clozaril-treated patients who experienced weekly WBC monitoring. These data will be used to update Figure C. Figure C provides estimates of various probabilities that will be used in the following steps for estimation of rates under less frequent monitoring options.

Step 2: The number of patients in Cohort 3 that would be "caught" or "missed" under less frequent monitoring will be estimated using the method described on pages 169-170 of the above-mentioned briefing book (Attachment 3).

Step 3: The projected number of cases of agranulocytosis and severe leukopenia will be estimated following the method used in Table D, page 33 of the above-mentioned briefing book (Attachment 4). The estimated probabilities obtained in Step 1 and the estimated number of cases "caught" and "missed" in Step 2 will be used in computation of rates.

Step 4: Finally, Tables similar to Tables E, F, G, and H, pages 34-37 of the above-mentioned briefing book (Attachment 5) will be produced for monthly or no-monitoring of WBC after six months, one year, and two years of Clozaril treatment.

Attachments

Attachment 1 **Definitions of Cohorts 1-3**

Attachment 2 **Figure C**

Attachment 3 **Pages 169-170**

Attachment 4 **Table D**

Attachment 5 **Tables E and F**

Tables G and H

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10. Appendix 3 Projected numbers of agranulocytosis and severe leukopenia cases

Post-text Table 4
Number of agranulocytosis and severe leukopenia cases projected to occur after change from bi-weekly monitoring for Cohort 3
(Excluded patients' data met criteria 1, 2 and 3)

	Change monitoring after	No. of cases: Bi-weekly (actual)	No. of cases: Monthly	No. of cases: No Monitoring	Patient Year	Rate per 1000 patient-years: Bi-weekly (actual)	Rate per 1000 patient-years: Monthly	Rate per 1000 patient-years: No Monitoring
Agran	Six months	7+	45	157	27017	0.26	1.68	5.81
	One year	2	28	88	17595	0.11	1.57	4.98
	Two years	0	9	34	6030	0.00	1.51	5.66
Severe	Six months	9	100	230	27017	0.33	3.68	8.51
Leukopenia	One year	5	61	128	17595	0.28	3.46	7.27
	Two years	4	20	50	6030	0.66	3.29	8.29

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before brand clozapine
Criteria 3: Patients started on brand clozapine, but switched to generic after Dec. 1, 97. All data will be excluded after the first generic clozapine

+ Excluded 3 patients with less than 6 months of treatment but the reporting date of agranulocytosis was more than 6 months from start of therapy.

Post-text Table 5

cumulative number* of agranulocytosis and severe leukopenia cases projected to occur beginning 6 months after initiation of Clozaril therapy, by timing of reduction in frequency of WBC monitoring for Cohort 3 (Excluded patients' data met criteria 1, 2 and 3)

	Change monitoring after	No. of cases Bi-weekly (actual)	No. of cases Monthly	No. of cases No Monitoring	Patient Year	Rate per 1000 patient-years Bi-weekly (actual)	Rate per 1000 patient-years Monthly	Rate per 1000 patient-years No Monitoring
Agran	Six months	7+	45	157	27017	0.26	1.68	5.81
	One year	7+	33	93	27017	0.26	1.21	3.43
	Two years	7+	16	41	27017	0.26	0.60	1.52
Severe Leukopenia	Six months	9	100	230	27017	0.33	3.68	8.51
	One year	9	65	132	27017	0.33	2.40	4.89
	Two years	9	25	55	27017	0.33	0.92	2.04

Criteria 1: Excluded patients with only one record of WBC
Criteria 2: Excluded patients suspected of starting with generic clozapine before brand clozapine
Criteria 3: Patients started on brand clozapine, but switched to generic after Dec. 1, 97. All data will be excluded after the first generic clozapine

* Actual number of cases occurred after 6 months of treatment and before change monitoring were added to the projected number of cases so that cumulative number of cases were comparable under different monitoring systems.

\+ Excluded 3 patients with less than 6 months of treatment but the reporting date of agranulocytosis was more than 6 months from start of therapy.

11. Appendix 4 Agranulocytosis rates in various monitoring schedules

Clozaril® (clozapine)

Australian, United Kingdom and United States Data

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Table Australian Data

	Weeks 0-18	Weeks 19-52	Weeks >52
Moderate Leukopenia {per 1,000 pt. yrs. (N)}	52.5 (165) weekly	11.8 (60) monthly	6.1 (165) monthly
Severe Leukopenia {per 1,000 pt. yrs. (N)}	12.7 (40) weekly	1.6 (8) monthly	0.7 (19) monthly
Agranulocytosis {per 1,000 pt. yrs. (N)}	8.3 (26) weekly	2.2 (11) monthly	0.5 (14) monthly

N – number of events

Table United Kingdom Data

	Weeks 0-18	Weeks 19-52	Weeks >52
Moderate Leukopenia (Red Alert) {per 1,000 pt. yrs. (N)}			
Pre-1995 (monitoring frequency)	104.6 (181) weekly	30.6 (79) bi-weekly	11.8 (77) bi-weekly
Post-1995 (monitoring frequency)	81.9 (478) weekly	20.7 (177) bi-weekly	7.4 (228) monthly
Severe Leukopenia {per 1,000 pt. yrs. (N)}			
Pre-1995 (monitoring frequency)	33.5 (58) weekly	4.3 (11) bi-weekly	2.6 (17) bi-weekly
Post-1995 (monitoring frequency)	31.9 (186) weekly	4.0 (34) bi-weekly	1.9 (58) monthly
Agranulocytosis {per 1,000 pt. yrs. (N)}			
Pre-1995 (monitoring frequency)	24.8 (43) weekly	1.2 (3) bi-weekly	0.3 (2) bi-weekly
Post-1995 (monitoring frequency)	20.4 (119) weekly	1.5 (13) bi-weekly	0.6 (18) monthly

Table United States Data

	Weeks 0-18	Weeks 19-52	Weeks >52
Moderate Leukopenia {per 1,000 pt. yrs. (N)}			
Pre-1998 (monitoring frequency)	35.3 (1470) weekly	13.8 (83) weekly	8.3 (2131) weekly
Post-1998 (monitoring frequency)	32.9 (345) weekly	10.6 (137) weekly/bi-weekly	7.2 (126) bi-weekly
Severe Leukopenia {per 1,000 pt. yrs. (N)}			
Pre-1998 (monitoring frequency)	8.8 (369) weekly	1.0 (66) weekly	0.4 (117) weekly
Post-1998 (monitoring frequency)	4.1 (43) weekly	0.7 (9) weekly/bi-weekly	0.3 (5) bi-weekly
Agranulocytosis {per 1,000 pt. yrs. (N)}			
Pre-1998 (monitoring frequency)	8.8 (366) weekly	0.8 (50) weekly	0.4 (101) weekly
Post-1998 (monitoring frequency)	3.8 (40) weekly	1.0 (14) weekly/bi-weekly	0.1 (2) bi-weekly